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Pharmacokinetics and Metabolism of Irinotecan Combined with Capecitabine in Patients with Advanced Colorectal Cancer

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Abstract. *Background: Irinotecan (CPT-11) in combination with 5-fluorouracil/folinic acid is used successfully for first-line treatment of metastatic colorectal cancer. Capecitabine (CCB) represents a very convenient alternative to 5-fluorouracil, either as single agent or in a combination of regimens acting synergistically and with the potential to further improve efficacy. Both CPT-11 and CCB need to be activated by human carboxyl esterases, therefore a probable pharmacokinetic drug interaction was checked. Patients and Methods: Ten patients suffering from advanced colorectal cancer were enrolled in this trial. CPT-11 was administered as a 30-min i.v.-infusion (70 mg/m^2) weekly. CCB was given p.o. twice daily for two weeks (2,000 mg/m^2 daily) starting the day after the first CPT-11 infusion. Plasma samples were analysed during/after the first (MONO) and third (CAPIRI) CPT-11 infusion. Results: CCB did not alter CPT-11 plasma disposition, and no significant changes in c_{max}, AUC_{last}, Vdss and Cl_{tot} during CAPIRI treatment could be observed. However, co-administration of CCB appeared to decrease SN-38 (the cytotoxic CPT-1l metabolite) plasma concentrations during the first three hours after initiation of CPT-11 infusion, with strongly time-dependent plasma percentage differences between control and CAPIRI treatment ($p<0.005$, $R=0.981$). Co-administration of CCB also had a similar impact on the initial plasma disposition of SN-38gluc, but not on that of the APC metabolite. Conclusion: Overall, our findings indicate that, while the administration of CCB resulted in reversible lower formation rates of SN-38 and SN-38gluc, it did not have a significant impact on CPT-11 pharmacokinetics.*

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The topoisomerase-I inhibitor irinotecan (CPT-11) is highly active as a single agent or when combined with 5-fluorouracil (5-FU)+leucovorin for patients with metastatic colorectal cancer (CRC). As first-line therapy, the combination of CPT-11 and 5-FU/LV significantly improves the response rate, time to disease progression and overall survival compared with 5-FU/LV alone (1, 2). Given the inconvenience, issues associated with administering 5-FU by continuous infusion (3), including increased patient and healthcare professional time compared with bolus regimens and the cost and risks associated with central venous catheters (4, 5), there is a clear rationale for combining CPT-11 with orally active alternatives to 5-FU. The oral fluoropyrimidine capecitabine (CCB) was designed to generate 5-FU preferentially within tumours and to mimic continuous infusions of 5-FU (6, 7), while being highly active and better tolerated than *i.v.* 5-FU (8, 9). Consequently, CCB is a promising and convenient alternative to 5-FU, either as a single agent or in a combination of regimens.

In nude mice colon cancer xenograft models, the combination of CCB and CPT-11 was significantly more active than either agent alone at its maximum tolerated dose (10). In addition, a number of phase I/II trials using different CCB/CPT-11 regimens demonstrated that replacing infusional 5-FU with CCB in combination with CPT-11 is a feasible, effective and well-tolerated option for the first-line treatment of patients with metastatic CRC (11-16).

CCB is rapidly and almost completely absorbed through the gastrointestinal wall, and is metabolised to 5-FU *via* a three-step enzymatic cascade (17, 18). The final step in this conversion of CCB to 5-FU is mediated by the enzyme thymidine phosphorylase (TP), which is highly active in tumour tissue compared with healthy tissues (6). 5-FU then undergoes anabolism in the tumour cell and catabolism to 5-fluoro-β-alanine.

CPT-11 acts as a precursor of the highly cytotoxic agent SN-38. Activation of the latter is a one-step reaction, catalysed by the isoenzymes of human carboxyl esterase

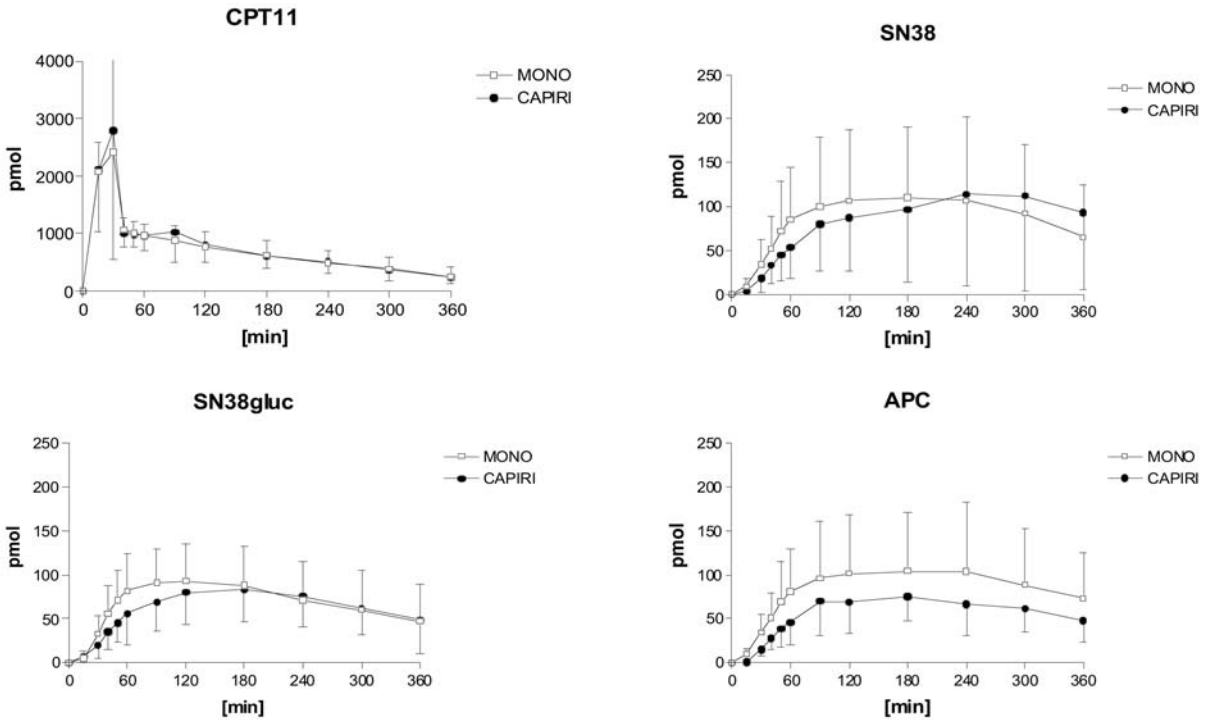

Figure 1. *Mean plasma concentration time curves (±SD) of CPT-11, SN-38, SN-38gluc and APC.*

(hCE) in the liver and intestine. SN-38 is subsequently eliminated by β-D-glucuronidation to SN-38 glucuronide (SN-38gluc). Other non-toxic metabolites of CPT-11 include APC (7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycampto- thecin) and NPC [7-ethyl-10-(4-amino-1-piperidino)-carbo-nyloxycamptothecin]. All metabolites are present in the blood and tissue in their lactone and carboxylate forms.

Recent data have shown that a pharmacokinetic (PK) drug interaction may occur between CPT-11 and some other antineoplastic drugs such as carboplatin (29), paclitaxel (31) and 5-FU (30). The metabolism of CPT-11 may be influenced by co-administration of drugs metabolised by the same enzymes (hCE, CYP3A4, UGT1A1). Concerning CCB as a combination partner, the current literature provides only few PK data for CPT-11 when given with CCB (11, 14). But, according to their known routes of metabolic activation, both drugs are metabolised simultaneously in the blood, and initially in the liver by hCE. Identification of any potential competitive interaction *via* hCE could, therefore, be important for the design of CPT-11/CCB combination schedules. Consequently, the primary objective of this study was to evaluate the disposition of CPT-11 and its metabolites SN-38, SN-38gluc and APC during treatment with weekly CPT-11 alone and when administered in a combination schedule with CCB.

Patients and Methods

Patients. Ten patients (2 female, 8 male), who received CPT-11 plus CCB for advanced CRC, entered the pharmacokinetic study. The mean age was 68±6 years (range 57-76 years), mean body mass ranged from 62 to 92 kg (78±12 kg), mean height was 174±7 cm (range 163-183 cm) and mean body surface area was 1.92 m^2 (range 1.66-2.1 m^2). Written informed consent was obtained from each patient according to the specifications of the ethics committee of the University of Vienna, Austria. Inclusion criteria were as follows: Karnofsky index >70%; white blood cell count >4,000/μl; WHO performance status of 1; no renal impairment as judged by standard biochemical parameters (plasma creatinine <1.5 mg/dl); and no hepatic impairment (bilirubin <0.6 mg/dl, γ-glutamyl-transferase <100 U/l and alaninaminotransferase <30 U/l).

Study design and treatment. The study had a prospective crossover design with patients serving as their own controls so as to minimize problems associated with interpatient variability. CPT-11 (Campto®) was supplied as a sterile solution containing 40 mg in 2-ml vials (Aventis Pharma, Vienna, Austria). CPT-11 was infused through a central venous catheter at a constant rate for 30 min every week (70 mg/m^2, mean total dose 134 mg, range 116.2-147.0 mg, mean infusion rate 4.47 mg/min) for 6 weeks, the first infusion being the control treatment. Premedication was tropisetron (5 mg) and dexamethasone (8 mg in 100 ml sodium chloride solution given as a 30-min *i.v.* infusion) 1 h before CPT-11 infusion.

CCB (Xeloda®) was obtained from Hoffmann La Roche (Vienna, Austria) as tablets containing 500 mg and 300 mg CCB. A

Table I. *Linear regression analysis for the percent difference of plasma concentrations between MONO and CAPIRI schedule versus time.*

Parameter	CPT-11	SN-38	SN-38gluc	APC
N	11	11	10	11
k	–0.024	0.234	0.181	–0.065
d	5.875	–48.772	–42.150	–17.770
corr	0.298	0.981	0.959	0.317
p	0.569	0.005	0.027	0.072

N number of data points
k slope of regression line
d intercept with Y-axis
corr correlation coefficient for the regression line
p *p* level of significance

dose of 1,000 mg/m^2 each was given twice daily (one dose 30 min after breakfast; the other 30 min after the evening meal) for 2 weeks starting the day after the first CPT-11 infusion.

Blood samples. Blood samples of 5 ml each were drawn from the cubital vein during the first cycle (day 1, MONO) and third cycle of therapy (day 15, CAPIRI) at the following times: 0,15, 30, 40, 50, 60, 90, 120, 180, 240, 300 and 360 min after start of infusion. Samples were collected in sodium-heparinised vacutubes, and red blood cells were separated by centrifuging at 2,500 rpm for 5 min. Sample clean-up was performed by vortexing 1.0 ml plasma with 3.0 ml of ice-cold methanol for 1 min, and precipitated proteins were removed by centrifuging at 10,000 rpm for 5 min. To obtain total lactone amounts, 1.0 ml of the supernatant was acidified with 50 µl phosphoric acid (6%) and frozen immediately at –80˚C until HPLC analysis.

Analytical procedure. CPT-11, SN-38, SN-38gluc and APC were quantified in samples by isocratic reversed-phase HPLC using fluorimetric detection, as described recently (19, 20).

Biometric calculations. WinNonlin version 4.1 (Pharsight Inc., USA) was used for curve fitting of plasma concentration data. A non-compartmental model for short continuous infusion (model 202) was chosen for PK modelling.

The following parameters were analysed for CPT-11:

t_{max} time to reach peak plasma concentration [min]
c_{max} peak plasma concentration [pmol]
AUC_{last} area under the concentration time-curve from 0 to 360 min [nmol*min]
Vdss volume of distribution at steady state [ml]
Cl_{tot} total body clearance [ml/min]
MRT mean residence time [min]
$t_{1/2}$last half-life to c_{last} [min]

The following PK parameters for SN-38, SN-38gluc and APC were calculated using the software "PKSolutions" version 1.1 (Summit Inc., USA).

$t_{1/2}$appin apparent half-life of formation [min]
t_{max} time to reach peak plasma concentration [min]
c_{max} peak plasma concentration [pmol]
AUC_{last} area under the plasma-concentration time-curve from 0 to 360 min [nmol*min]
$t_{1/2}$last half-life to c_{last} [min]

Table II. *PK parameters for CPT-11, SN-38, SN-38gluc and APC.*

CPT-11	MONO mean	sd	CAPIRI mean	sd
t_{max}	24	8	27	6
c_{max}	2597	1838	2948	2198
AUC_{last}	225	58.5	245.9	80
$t_{1/2}$last	175	81	183	64
Vdss	161	32	162	49
Cl_{tot}	838	325	773	305
MRT_{last}	94	16	97	12
SN-38	**MONO mean**	**sd**	**CAPIRI mean**	**sd**
$t_{1/2}$appin	27.8	11.9	37.9	20.1
$t_{1/2}$last	452.1	363.9	427	303.2
c_{max}	84.8	35.7	111.6	114
t_{max}	108	35.2	126	31
$AUC_{0\text{-}300}$	20.1	12.4	22.2	19.5
SN-38gluc	**MONO mean**	**sd**	**CAPIRI mean**	**sd**
$t_{1/2}$appin	25	9.6	42.3 *	12.5
$t_{1/2}$last	255.6	170.6	293.3	163.8
c_{max}	102	42.6	92.2	39.7
t_{max}	108	32.2	150.0 *	31.6
$AUC_{0\text{-}300}$	21.6	10.7	19.4	8.6
APC	**MONO mean**	**sd**	**CAPIRI mean**	**sd**
$t_{1/2}$appin	29.9	10.6	37.1	18.4
$t_{1/2}$last	501.1	nc	417.4	nc
c_{max}	104.4	66.8	75.4	27.2
t_{max}	165	58.7	185	42.7
$AUC_{0\text{-}300}$	25.4	9.8	17.1	8.5

*$p<0.05$

Linear regression analysis was used to analyse the time dependence between differences of plasma concentrations (CAPIRI minus MONO) *versus* time after start of infusion. Statistical evaluation of differences in plasma concentrations and PK parameters were performed using paired, two-sided Student's *t*-test. All statistical analyses were calculated by use of the software Graph Pad Prism® 4.0 for Windows.

To obtain the percent AUC amount of metabolite [AUC_{met}], the AUC_{last} values of each metabolite (SN-38, SN-38gluc or APC) were compared with the sum of AUCs as follows:

$$AUC_{met}\,[\%] = \frac{AUC_{met} * 100}{AUC_{CPT\text{-}11\,+\,SN\text{-}38\,+\,SN\text{-}38gluc\,+\,APC}}$$

An apparent formation-coefficient [R] of the metabolites catalysed by CYP3A4, hCE and UGT1A1, respectively, has been calculated by dividing the metabolite AUC_{last} by its precursors AUC_{last}:

$$R_{CYP3A4} = \frac{AUC_{APC}}{AUC_{CPT11}}$$

$$R_{hCE} = \frac{AUC_{SN38}}{AUC_{CPT11}}$$

$$R_{UGT1A1} = \frac{AUC_{SN38gluc}}{AUC_{SN38}}$$

Table III. *Metabolic ratio [R_{met}] for APC, SN-38 and SN-38gluc.*

Enzyme	Metabolite	MONO	CAPIRI	diff [%]
R_{CYP3A4}	APC	0.113	0.069	–39
R_{hCE}	SN-38	0.089	0.090	+1
R_{UGT1A1}	SN-38gluc	1.075	0.874	–29

Diff. percent change of metabolic ration

Results

Plasma concentrations. One of the major impediments in the analysis of CPT-11 concentrations is the continuous interconversion of the lactone into the carboxylate form in human plasma. Equilibrium is attained within 5-6 h, with approximately 15% of the drug existing as the lactone, although high interpatient variability represents a source of error when evaluating the PK of CPT-11 and SN-38. However, we assumed an equal CPT-11 equilibrium and monitored the total drug concentrations for all analytes as recommended (21).

Mean plasma concentration-time curves for CPT-11 were almost identical during MONO and CAPIRI treatment (Figure 1). Minor differences in CPT-11 concentrations were observed for the 30- to 90-min samples (–15%; $p<0.569$).

SN-38 was already detectable 15 min after the onset of CPT-11 infusion. In contrast to MONO, the mean plasma concentrations of SN-38 were lower during CAPIRI treatment (Figure 1) without significance. The plasma concentration, however, differed in a time-dependent manner from –53% at 15 min (after the onset of infusion) to –12% at 180 min. At 240 and 300 min an inverse effect was observed (+6 and +23%, respectively). Linear regression analysis of differences in SN-38 concentration *versus* time revealed a strong dependence and could be expressed as: difference [%] = 0.234* min –48.8.

The phase-II conjugate SN-38gluc was detected in plasma within 30 min of starting the infusion and reached its maximum plasma concentrations after 120 min, during CPT-11 alone, and after 180 min during CAPIRI treatment (Table I). SN-38gluc is eliminated *via* the faecal route, so the plasma level represented only that portion that has been redistributed into the blood. In the presence of CCB, SN-38gluc plasma concentrations were reduced reversibly in a time-dependent manner. Differences were –39% at 15 min after the start of CAPIRI treatment and decreased to –4% at 180 min (Table I). Using regression analysis, linear dependence could also be calculated for these SN-38gluc differences, as listed in Table I.

The plasma concentrations of APC were of a similar order of magnitude as those of SN-38 and SN-38gluc; in the CAPIRI treatment there were also lower plasma concentrations. However, contrary to SN-38 and SN-38gluc, these observed differences between MONO and CAPIRI treatment were not reversible and remained at –37% at 6 h after the start of infusion.

Pharmacokinetics. PK parameters of CPT-11 and its metabolites were calculated from the data obtained under acidic analytical conditions (only lactones in the samples). Due to the limited sampling period of 6 h, $t_{1/2}$lambdaZ did not represent the true half-life of elimination. Therefore, MRT and AUC values are only presented as their "last" values. Comparison of AUC_{last} values for CPT-11, SN-38, SN-38gluc and APC with the sum of AUCs revealed no significant difference between MONO and CAPIRI treatment.

The PK parameters of CPT-11, SN-38, SN-38gluc and APC are summarized in Table II. No significant differences in c_{max} or AUC_{last} between MONO and CAPIRI treatment could be observed. The mean $t_{1/2}$appin of metabolites was increased by CCB from 24 to 69% and was significant in the case of SN-38gluc. Accordingly, mean t_{max} values were numerically higher during CAPIRI treatment compared with MONO.

The apparent half-lives of formation of SN-38 and APC were slower in the CAPIRI treatment, but without significance. In contrast, SN-38gluc half-life was significantly lower during CAPIRI treatment: 42±12 min (range 25-65 min) *vs.* 25±10 min (range 10-40 min, $p<0.0036$). This decrease might indicate a delayed redistribution to the plasma. As a consequence, t_{max} was higher during CAPIRI treatment, although the other parameters did not differ significantly.

Dividing the product AUC_{last} by the precursor AUC_{last} makes it possible to estimate a specific activity of the enzyme that catalyses the product formation. As listed in Table III, the metabolic ratio of hCE is not affected by CCB, but the activity of CYP3A4 and UGT1A1 seemed to be reduced by about 39 and 29%, respectively.

Pharmacology data. The aim of this PK study was to determine the plasma disposition of CPT-11 and its main metabolites in patients receiving chemotherapy with weekly CPT-11 alone and with CCB (CAPIRI schedule) after three

weeks. While we did not set out to evaluate antitumour response, efficacy data were collected in this group of patients. Three of the 13 patients enrolled were excluded from the PK analysis as a result of disease progression. Of the remaining 10 patients, one received first-line therapy, and this subject showed a partial tumour response. The other 9 patients had been pretreated with oxaliplatin and received the CAPIRI schedule as a second-line treatment; during therapy no change of tumour response was evaluable. Dose reduction of CPT-11 was not necessary, because no grade 3/4 adverse events (haematological events or hand-foot syndrome) could be observed.

Discussion

The PK profile of CPT-11 is rather complex as a result of the multiple biotransformation pathways involving various enzymes (hCE, CYP3A4, UGT1A1). This is further complicated by the interconversion of CPT-11 lactone and carboxylate forms in the presence of protein. The equilibrium of lactone-carboxylate forms of CPT-11 and its active metabolite SN-38 depend, on the pH of the solution: pH values higher than 7.0 tend to result in the carboxylate form. However, assuming an equal CPT-11 equilibrium in our study, it appears unlikely that CCB shifts that lactone-carboxylate equilibrium. Consequently, the total drug concentrations for all analytes were monitored as recommended (21).

As a carbamate, CPT-11 is a relatively poor substrate for hCE (22). This is thought to be the result of slow decarbamylation of the serine esteratic site of hCE, inferring that CPT-11 is a weekly competitive inhibitor. Assuming that there is some type of PK interaction, it is possible that CPT-11 could be inhibited by xenobiotic high turnover substrates of hCE, such as CCB, which is rapidly metabolised by hCE (22, 23). Generally, the low affinity of CPT-11 for hCE only generates small amounts of the active SN-38 lactone in the body (30-100 pmol). Nevertheless, because of the high antitumour activity of SN-38 (approximately 100-1,000 times that of CPT-11), these concentrations are sufficient for an effective anticancer therapy.

Recently, it has been demonstrated that the administration sequence of CPT-11 and 5-FU affects the formation of SN-38. AUC values of SN-38 were shown to be approximately 40% lower ($p<0.05$) when 5-FU bolus preceded CPT-11 (24). It was also found that administration of CCB resulted in continuous formation of small amounts of 5-FU ($\sim$300 ng/ml) (26). Fluorine, which is formed rapidly by the catabolism of the 5-FU metabolite FBAL, is a known hCE- inhibitor (25) and has been found to inhibit a range of enzymes, including microsomal and blood esterases, various phosphatases, acetylcholinesterase and others (23). These observations are a probable explanation for the observed lower AUC of SN-38 after 5-FU bolus. Nevertheless, these minor interactions between CPT-11 and 5-FU have not prevented the development and investigation of various CPT-11/5-FU combination regimens, and the same can be expected with CPT-11/CCB regimens.

It is important to acknowledge the low dose of CPT-11 (70 mg/m^2) used in our study, which resulted in very small plasma concentrations of SN-38 that were occasionally at the limit of quantification.

In a recently presented study of CCB in combination with 3-weekly CPT-11 (XELIRI regimen) as first-line treatment in 57 patients with metastatic CRC, there were no statistically significant pharmacokinetic interactions, and the regimen demonstrated promising efficacy (response rate, 47%) and good tolerability (14). Similar findings from a smaller French study of the XELIRI regimen have also been presented (12).

In conclusion, while the co-administration of CCB resulted in a lower formation rate of SN-38, it did not have a significant impact on the plasma concentrations of CPT-11. Our data, showing that the PK of CPT-11 is not altered by the concomitant administration of CCB, is consistent with previous findings with the 3-weekly XELIRI regimen (14). However, it is important to note that the weekly administration of CPT-11 we studied differs from the standard 3-weekly schedule. Nevertheless, the feasibility, activity and good tolerability of the CAPIRI regimen would be expected to completely override any potential PK interactions between the two drugs. These, together with the findings from other preclinical and clinical studies, provide a strong rationale for further evaluation of sequential CAPIRI schedules in patients with advanced/metastatic CRC. From the PK point of view, the weekly Campto/Xeloda schedule seems to be safe, and the data prove that there is no clinically relevant drug interaction with a weekly Campto®/Xeloda® regimen. In future studies, administration of a higher CPT-11 dose (*e.g.* 120 mg/m^2), that generates higher levels of SN-38, would be helpful in elucidating the effects of concomitant CCB administration.

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